CLAIMS

1. A pharmaceutical composition comprising effective amounts of pharmacologically active agents, wherein said pharmacologically active agents comprise:

(a) an anti-human Fas antibody having an apoptosis inducing activity; and

(b) a compound having a folate antagonistic activity or a dihydrofolate reductase inhibiting activity,

the relative amounts of said active ingredients (a) and (b) being such that they exhibit a synergistic apoptosis inducing activity.

2. The pharmaceutical composition according to claim 1, wherein said anti-human Fas antibody having apoptosis inducing activity is a monoclonal antibody CH11, HFE7A or a humanized antibody thereof.

3. The pharmaceutical composition according to claim 1, wherein said anti-human Fas antibody having apoptosis inducing activity is a monoclonal antibody CH11 or a humanized antibody thereof.

4. The pharmaceutical composition according to claim 1, wherein said anti-human Fas antibody having apoptosis inducing activity is an anti-human Fas monoclonal antibody HFE7A produced by a mouse-mouse hybridoma HFE7A (FERM BP-5828) or a humanized antibody thereof.

5. The pharmaceutical composition according to claim 1, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is selected from the group consisting of methotrexate, edatrexate, epiroprim, iometrexol, pyritrexim, trimetrexate, brodimoprim, MX-68, N-[4-[3-(2,4-diamino-6,7-dihydro-5H-cyclopenta[d]-pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]carbonyl]-L-glutamic acid, (R)-N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]-carbonyl]-L-glutamic acid, N-((2,4-diamino-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-6-yl)ethyl)-2-thienylcarbonyl-L-glutamic acid, (S)-2-[[[4-carboxy-4-[[4-[[(2,4-diamino-6-pteridinyl)methyl]amino]benzoyl]amino]butyl]amino]carbonyl]benzoic acid, N-[4-[3-(2,4-diamino-1H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, 2,4-diamino-6-

(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline, 2,4-diamino-5-[4-[3-(4-aminophenyl-4-sulfonylphenylamino)propoxy]-3,5-dimethoxybenzyl]pyrimidine, N-[4-[4-(2,4-diamino-5-pyrimidinyl)butyl]benzoyl]-L-glutamic acid, N-[4-[3-(2,4-diamino-5-pyrimidinyl)propyl]benzoyl]-L-glutamic acid, N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]-benzoyl]-4-methylene-DL-glutamic acid and N-(1-methylethyl)-N'[3-(2,4,5-trichlorophenoxy)propoxy]imidodicarbonimidic diamide hydrochloride (PS15).

6. The pharmaceutical composition according to claim 2, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is selected from the group consisting of methotrexate, edatrexate, epiroprim, iometrexol, pyritrexim, trimetrexate, brodimoprim, MX-68, N-[4-[3-(2,4-diamino-6,7-dihydro-5H-cyclopenta[d]-pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]carbonyl]-L-glutamic acid, (R)-N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]-carbonyl]-L-glutamic acid, N-((2,4-diamino-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-6-yl)ethyl)-2-thienylcarbonyl-L-glutamic acid, (S)-2-[[[4-carboxy-4-[[4-[[(2,4-diamino-6-pteridinyl)methyl]amino]benzoyl]amino]butyl]amino]carbonyl]benzoic acid, N-[4-[3-(2,4-diamino-1H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, 2,4-diamino-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline, 2,4-diamino-5-[4-[3-(4-aminophenyl-4-sulfonylphenylamino)propoxy]-3,5-dimethoxybenzyl]pyrimidine, N-[4-[4-(2,4-diamino-5-pyrimidinyl)butyl]benzoyl]-L-glutamic acid, N-[4-[3-(2,4-diamino-5-pyrimidinyl)propyl]benzoyl]-L-glutamic acid, N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]-benzoyl]-4-methylene-DL-glutamic acid and N-(1-methylethyl)-N'[3-(2,4,5-trichlorophenoxy)propoxy]imidodicarbonimidic diamide hydrochloride (PS15).

7. The pharmaceutical composition according to claim 3, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is selected from the group consisting of methotrexate, edatrexate, epiroprim, iometrexol, pyritrexim, trimetrexate, brodimoprim, MX-68, N-[4-[3-(2,4-diamino-6,7-dihydro-5H-cyclopenta[d]-pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]carbonyl]-L-glutamic acid, (R)-N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]-carbonyl]-L-glutamic acid, N-((2,4-diamino-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-6-yl)ethyl)-2-thienylcarbonyl-L-glutamic acid, (S)-2-[[[4-carboxy-4-[[4-[[(2,4-diamino-6-

pteridinyl)methyl]amino]benzoyl]amino]butyl]amino]carbonyl]benzoic acid, N-[4-[3-(2,4-diamino-1H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, 2,4-diamino-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline, 2,4-diamino-5-[4-[3-(4-aminophenyl-4-sulfonylphenylamino)propoxy]-3,5-dimethoxybenzyl]pyrimidine, N-[4-[4-(2,4-diamino-5-pyrimidinyl)butyl]benzoyl]-L-glutamic acid, N-[4-[3-(2,4-diamino-5-pyrimidinyl)propyl]benzoyl]-L-glutamic acid, N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]-benzoyl]-4-methylene-DL-glutamic acid and N-(1-methylethyl)-N'[3-(2,4,5-trichlorophenoxy)propoxy]imidodicarbonimidic diamide hydrochloride (PS15).

8. The pharmaceutical composition according to claim 4, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is selected from the group consisting of methotrexate, edatrexate, epiroprim, iometrexol, pyritrexim, trimetrexate, brodimoprim, MX-68, N-[4-[3-(2,4-diamino-6,7-dihydro-5H-cyclopenta[d]-pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]carbonyl]-L-glutamic acid, (R)-N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]-carbonyl]-L-glutamic acid, N-((2,4-diamino-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-6-yl)ethyl)-2-thienylcarbonyl-L-glutamic acid, (S)-2-[[[4-carboxy-4-[[4-[[(2,4-diamino-6-pteridinyl)methyl]amino]benzoyl]amino]butyl]amino]carbonyl]benzoic acid, N-[4-[3-(2,4-diamino-1H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, 2,4-diamino-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline, 2,4-diamino-5-[4-[3-(4-aminophenyl-4-sulfonylphenylamino)propoxy]-3,5-dimethoxybenzyl]pyrimidine, N-[4-[4-(2,4-diamino-5-pyrimidinyl)butyl]benzoyl]-L-glutamic acid, N-[4-[3-(2,4-diamino-5-pyrimidinyl)propyl]benzoyl]-L-glutamic acid, N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]-benzoyl]-4-methylene-DL-glutamic acid and N-(1-methylethyl)-N'[3-(2,4,5-trichlorophenoxy)propoxy]imidodicarbonimidic diamide hydrochloride (PS15).

9. The pharmaceutical composition according to claim 1, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is methotrexate.

10. The pharmaceutical composition according to claim 2, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is methotrexate.

11. The pharmaceutical composition according to claim 3, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is methotrexate.

12. The pharmaceutical composition according to claim 4, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is methotrexate.

13. A pharmaceutical composition in the form of a solution comprising effective amounts of pharmacologically active agents together with a diluent therefor, wherein said pharmacologically active agents comprise:

(a) an anti-human Fas antibody having apoptosis inducing activity selected from the group consisting of a monoclonal antibody CH11 and HFE7A, or a humanized antibody thereof in a concentration of 0.1 to 100 ng/ml; and

(b) methotrexate in a concentration of 0.05 to 5 nM,

the relative amounts of said active ingredients (a) and (b) being such that they exhibit a synergistic apoptosis inducing activity.

14. A method for the prevention or treatment of a disease preventable or treatable by an agent having apoptosis inducing activity, comprising administering to a mammal in need thereof effective amounts of:

(a) an anti-human Fas antibody having an apoptosis inducing activity; and

(b) a compound having a folate antagonistic activity or a dihydrofolate reductase inhibiting activity,

the relative amounts of the active ingredients (a) and (b) administered being such that they exhibit a synergistic apoptosis inducing activity.

15. The method according to claim 14, wherein the mammal is a human.

16. The method according to claim 15, wherein said anti-human Fas antibody having apoptosis inducing activity is a monoclonal antibody CH11, HFE7A or a humanized antibody thereof.

17. The method according to claim 15, wherein said anti-human Fas antibody having apoptosis inducing activity is a monoclonal antibody CH11 or a humanized antibody thereof.

18. The method according to claim 15, wherein said anti-human Fas antibody having apoptosis inducing activity is an anti-human Fas monoclonal antibody HFE7A produced by a mouse-mouse hybridoma HFE7A (FERM BP-5828) or a humanized antibody thereof.

19. The method according to claim 15, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is selected from the group consisting of methotrexate, edatrexate, piroprim, iometrexol, pyritrexim, trimetrexate, brodimoprim, MX-68, N-[4-[3-(2,4-diamino-6,7-dihydro-5H-cyclopenta[d]-pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]carbonyl]-L-glutamic acid, (R)-N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]-carbonyl]-L-glutamic acid, N-((2,4-diamino-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-6-yl)ethyl)-2-thienylcarbonyl-L-glutamic acid, (S)-2-[[[4-carboxy-4-[[4-[[(2,4-diamino-6-pteridinyl)methyl]amino]benzoyl]amino]butyl]amino]carbonyl]benzoic acid, N-[4-[3-(2,4-diamino-1H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, 2,4-diamino-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline, 2,4-diamino-5-[4-[3-(4-aminophenyl-4-sulfonylphenylamino)propoxy]-3,5-dimethoxybenzyl]pyrimidine, N-[4-[4-(2,4-diamino-5-pyrimidinyl)butyl]benzoyl]-L-glutamic acid, N-[4-[3-(2,4-diamino-5-pyrimidinyl)propyl]benzoyl]-L-glutamic acid, N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]-benzoyl]-4-methylene-DL-glutamic acid and N-(1-methylethyl)-N'[3-(2,4,5-trichlorophenoxy)propoxy]imidodicarbonimidic diamide hydrochloride (PS15).

20. The method according to claim 16, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is selected from the group consisting of methotrexate, edatrexate, piroprim, iometrexol, pyritrexim, trimetrexate, brodimoprim, MX-68, N-[4-[3-(2,4-diamino-6,7-dihydro-5H-cyclopenta[d]-pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]carbonyl]-L-glutamic acid, (R)-N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]-carbonyl]-L-glutamic acid, N-((2,4-diamino-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-

6-yl)ethyl)-2-thienylcarbonyl-L-glutamic acid, (S)–2-[[[4-carboxy-4-[[4-[[(2,4-diamino-6-pteridinyl)methyl]amino]benzoyl]amino]butyl]amino]carbonyl]benzoic acid, N-[4-[3-(2,4-diamino-1H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, 2,4-diamino-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline, 2,4-diamino-5-[4-[3-(4-aminophenyl-4-sulfonylphenylamino)propoxy]-3,5-dimethoxybenzyl]pyrimidine, N-[4-[4-(2,4-diamino-5-pyrimidinyl)butyl]benzoyl]-L-glutamic acid, N-[4-[3-(2,4-diamino-5-pyrimidinyl)propyl]benzoyl]-L-glutamic acid, N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]-benzoyl]-4-methylene-DL-glutamic acid and N-(1-methylethyl)-N'[3-(2,4,5-trichlorophenoxy)propoxy]imidodicarbonimidic diamide hydrochloride (PS15).

21. The method according to claim 17, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is selected from the group consisting of methotrexate, edatrexate, piroprim, iometrexol, pyritrexim, trimetrexate, brodimoprim, MX-68, N-[4-[3-(2,4-diamino-6,7-dihydro-5H-cyclopenta[d]-pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]carbonyl]-L-glutamic acid, (R)-N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]-carbonyl]-L-glutamic acid, N-((2,4-diamino-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-6-yl)ethyl)-2-thienylcarbonyl-L-glutamic acid, (S)–2-[[[4-carboxy-4-[[4-[[(2,4-diamino-6-pteridinyl)methyl]amino]benzoyl]amino]butyl]amino]carbonyl]benzoic acid, N-[4-[3-(2,4-diamino-1H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, 2,4-diamino-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline, 2,4-diamino-5-[4-[3-(4-aminophenyl-4-sulfonylphenylamino)propoxy]-3,5-dimethoxybenzyl]pyrimidine, N-[4-[4-(2,4-diamino-5-pyrimidinyl)butyl]benzoyl]-L-glutamic acid, N-[4-[3-(2,4-diamino-5-pyrimidinyl)propyl]benzoyl]-L-glutamic acid, N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]-benzoyl]-4-methylene-DL-glutamic acid and N-(1-methylethyl)-N'[3-(2,4,5-trichlorophenoxy)propoxy]imidodicarbonimidic diamide hydrochloride (PS15).

22. The method according to claim 18, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is selected from the group consisting of methotrexate, edatrexate, piroprim, iometrexol, pyritrexim, trimetrexate, brodimoprim, MX-68, N-[4-[3-(2,4-diamino-6,7-dihydro-5H-cyclopenta[d]-pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, N-[[5-[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]carbonyl]-L-glutamic acid, (R)-N-[[5-

[2-(2-amino-1,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-d]pyrimidin-6-yl)ethyl]-2-thienyl]-carbonyl]-L-glutamic acid, N-((2,4-diamino-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-6-yl)ethyl)-2-thienylcarbonyl-L-glutamic acid, (S)-2-[[[4-carboxy-4-[[4-[[(2,4-diamino-6-pteridinyl)methyl]amino]benzoyl]amino]butyl]amino]carbonyl]benzoic acid, N-[4-[3-(2,4-diamino-1H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]-L-glutamic acid, 2,4-diamino-6-(N-(4-(phenylsulfonyl)benzyl)methylamino)quinazoline, 2,4-diamino-5-[4-[3-(4-aminophenyl-4-sulfonylphenylamino)propoxy]-3,5-dimethoxybenzyl]pyrimidine, N-[4-[4-(2,4-diamino-5-pyrimidinyl)butyl]benzoyl]-L-glutamic acid, N-[4-[3-(2,4-diamino-5-pyrimidinyl)propyl]benzoyl]-L-glutamic acid, N-[4-[2-(2,4-diamino-6-pteridinyl)ethyl]-benzoyl]-4-methylene-DL-glutamic acid and N-(1-methylethyl)-N'[3-(2,4,5-trichlorophenoxy)propoxy]imidodicarbonimidic diamide hydrochloride (PS15).

23. The method according to claim 15, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is methotrexate.

24. The method according to claim 16, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is methotrexate.

25. The method according to claim 17, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is methotrexate.

26. The method according to claim 18, wherein said compound having a folate antagonist activity or a dihydrofolate reductase inhibiting activity is methotrexate.

27. The method according to claim 15, wherein the anti-human Fas antibody is administered in a daily dosage of 0.001 to 10 mg/kg and the compound having a folate antagonistic activity or a dihydrofolate reductase inhibiting activity is administered in a daily dosage of 0.15 µg/kg to 0.15 mg/kg.

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28. A method for the prevention or treatment of a disease preventable or treatable by an agent having apoptosis inducing activity, comprising administering to a mammal in need thereof effective amounts of a medicament in the form of a solution comprising pharmacologically active agents together with a diluent therefor, wherein said pharmacologically active agents comprise:

(a) an anti-human Fas antibody having apoptosis inducing activity selected from the group consisting of a monoclonal antibody CH11 and HFE7A, or a humanized antibody thereof in a concentration of 0.1 to 100 ng/ml; and

(b) methotrexate at a concentration of 0.05 to 5 nM,

the relative amounts of said active ingredients (a) and (b) being such that they exhibit a synergistic apoptosis inducing activity.

29. The method according to claim 28, wherein the mammal is a human.

30. The method according to claim 15, wherein said disease is an autoimmune disease or rheumatoid arthritis.

31. The method according to claim 16, wherein said disease is an autoimmune disease or rheumatoid arthritis.

32. The method according to claim 17, wherein said disease is an autoimmune disease or rheumatoid arthritis.

33. The method according to claim 18, wherein said disease is an autoimmune disease or rheumatoid arthritis.

34. The method according to claim 19, wherein said disease is an autoimmune disease or rheumatoid arthritis.

35. The method according to claim 20, wherein said disease is an autoimmune disease or rheumatoid arthritis.

36. The method according to claim 21, wherein said disease is an autoimmune disease or rheumatoid arthritis.

37. The method according to claim 22, wherein said disease is an autoimmune disease or rheumatoid arthritis.

38. The method according to claim 23, wherein said disease is an autoimmune disease or rheumatoid arthritis.

39. The method according to claim 24, wherein said disease is an autoimmune disease or rheumatoid arthritis.

40. The method according to claim 25, wherein said disease is an autoimmune disease or rheumatoid arthritis.

41. The method according to claim 26, wherein said disease is an autoimmune disease or rheumatoid arthritis.

42. The method according to claim 27, wherein said disease is an autoimmune disease or rheumatoid arthritis.

43. The method according to claim 28, wherein said disease is an autoimmune disease or rheumatoid arthritis.